C/O BEVERLY

Access DB# 119453

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: AUDET Examiner # : 7480[illegible] Date: 4/12/04
Art Unit: 1654 Phone Number 30[illegible] Serial Number: 10/[illegible]6936
Mail Box and Bldg/Room Location: REM 3D20 Results Format Preferred (circle): PAPER DISK E-MAIL
REM 3D11

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: →

Inventors (please provide full names): →

Earliest Priority Filing Date: 8/22/96

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search

1) 3 compound of CLAIM 30 (note: [illegible] [illegible] core A. acid structure. If free of art can cease further searching, but some small may be [illegible]), attached to 2nd search [illegible] structure w/ either ABC of CLAIM 31 - if free of art, no more searching needed
3rd if not [illegible] 2nd step, search compound w/ any of APC of CLAIM 32.

2) Inventor search

Tx Beverly, MAURY

****

STAFF USE ONLY	**Type of Search**	**Vendors and cost where applicable**
Searcher: Beverly C 2528	NA Sequence (#)	STN ✓
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed: 04-15-04	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

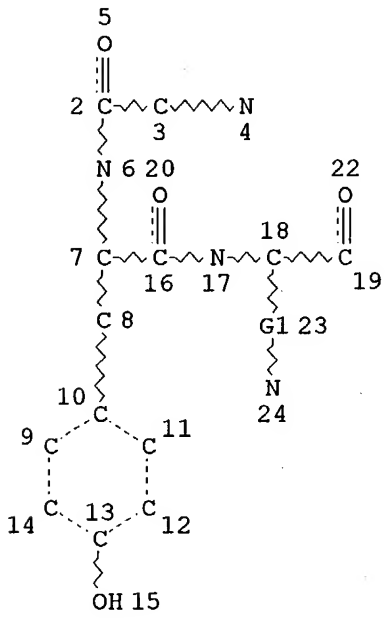
PTO-1590 (8-01)

Audet, M.
10/686436

(FILE 'REGISTRY' ENTERED AT 09:00:42 ON 15 APR 2004)

L1 STR

str.



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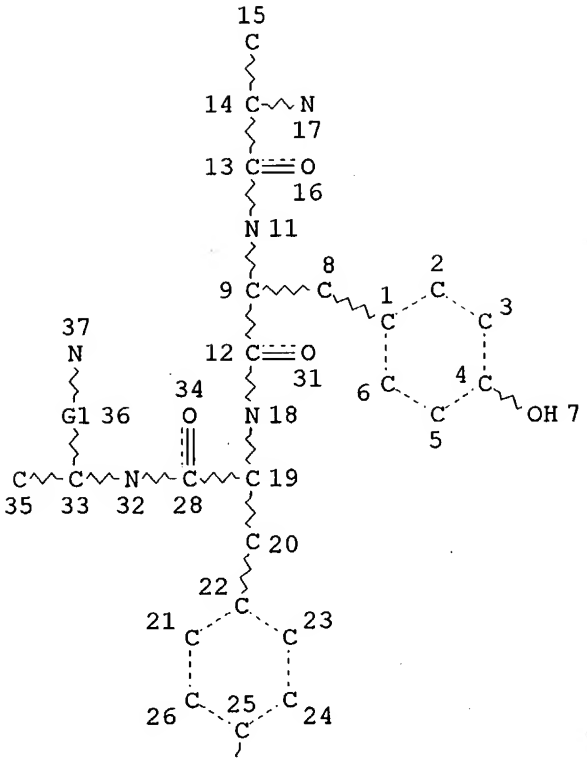

Page 1-A

OH 27

Page 2-A
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STEREO ATTRIBUTES: NONE
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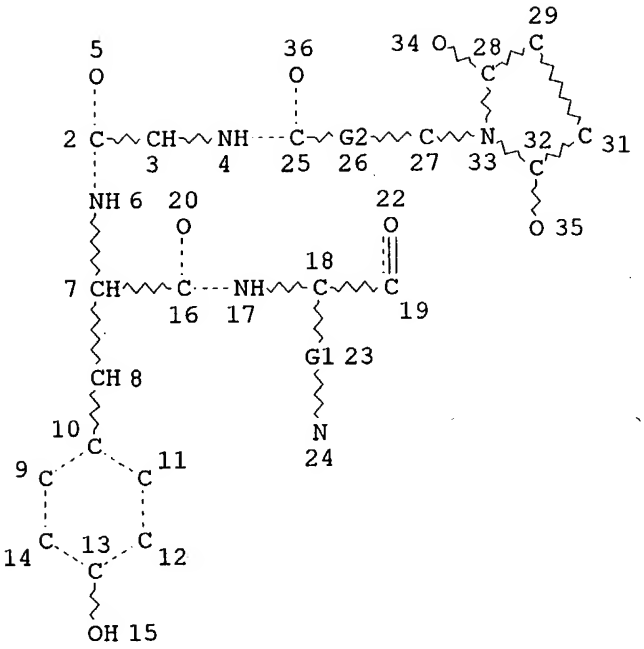

Str. 1

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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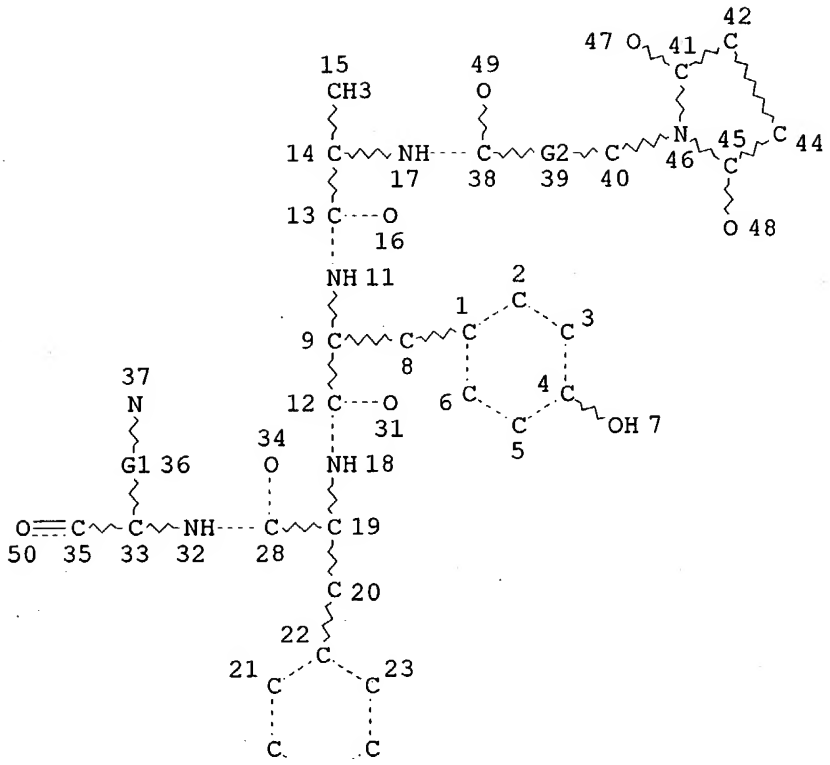

Strs. 1 & 2

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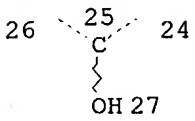

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 46

STEREO ATTRIBUTES: NONE
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FILE 'HCAPLUS' ENTERED AT 09:35:13 ON 15 APR 2004
L9 7 S L8

L9 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

Searcher : Shears 571-272-2528

ACCESSION NUMBER: 2003:980784 HCAPLUS
DOCUMENT NUMBER: 140:47476
TITLE: Stable radioiodine conjugates and methods for their synthesis
INVENTOR(S): Govindan, Serengulam V.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,558,669.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6663866	B1	20031216	US 2000-605873	20000629
US 6558669	B1	20030506	US 1997-919477	19970828
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1299129	A2	20030409	EP 2001-950673	20010629
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US 2003220470	A1	20031127	US 2003-359276	20030206
US 2004018148	A1	20040129	US 2003-395718	20030325
US 2004022725	A1	20040205	US 2003-411370	20030411

PRIORITY APPLN. INFO.:

US 1996-24738P	P	19960828
US 1997-919477	A2	19970828
WO 1997-US14998	A	19970827
EP 1997-954212	A3	19971219
WO 1997-US23711	A	19971219
US 2000-605873	A	20000629
US 2000-696740	A2	20001026
WO 2001-US20764	W	20010629

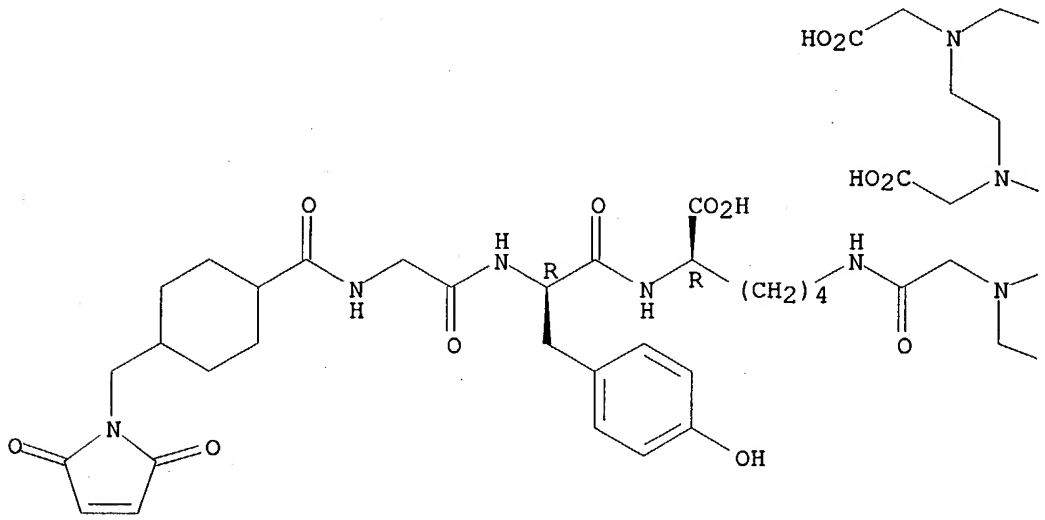
AB Methods are described for conjugating radioiodinated peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. Radioiodinated residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant radioiodinated residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy of tumors.

IT **634907-72-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT (Reactant or reagent)
(radioiodinated antibody conjugates)
RN 634907-72-5 HCAPLUS
CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]-1-[(4-isothiocyanatophenyl)methyl]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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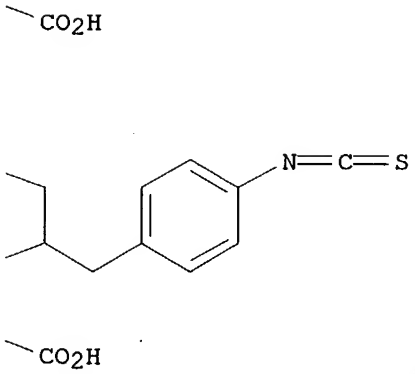


REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 571-272-2528

L9 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:719518 HCAPLUS
DOCUMENT NUMBER: 139:259962
TITLE: Humanized murine anti-epithelial glycoprotein 1 (EGP-1) antibodies RS7 and conjugates for diagnosis and treatment of cancer
INVENTOR(S): Govindan, Serengulam; Qu, Zhengxing; Hansen, Hans J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; Mccall, John Douglas
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074566	A2	20030912	WO 2003-GB885	20030303
WO 2003074566	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004001825	A1	20040101	US 2003-377121	20030303

PRIORITY APPLN. INFO.: US 2002-360229P P 20020301

AB This invention relates to monovalent and multivalent, monospecific binding proteins and to multivalent, multispecific binding proteins. One embodiment of these binding proteins has one or more binding sites where each binding site binds with a target antigen or an epitope on a target antigen. Another embodiment of these binding proteins has two or more binding sites where each binding site has affinity towards different epitopes on a target antigen or has affinity towards either a target antigen or a hapten. The present invention further relates to recombinant vectors useful for the expression of these functional binding proteins in a host. More specifically, the present invention relates to the tumor-associated antigen binding protein designated RS7, and other EGP-1 binding-proteins. The invention further relates to humanized, human and chimeric RS7 antigen binding proteins, and the use of such binding proteins in diagnosis and therapy.

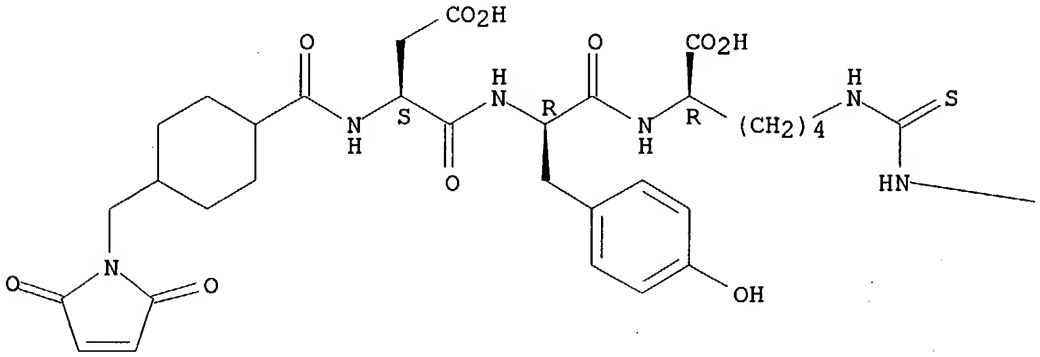
IT **588709-17-5D**, antibody conjugates
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized murine anti-EGP-1 antibodies RS7 and conjugates for diagnosis and treatment of cancer)

RN 588709-17-5 HCAPLUS
CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-

yl)methyl]cyclohexyl]carbonyl]-L-α-aspartyl-D-tyrosyl-N6-[[[4-[2-[bis(carboxymethyl)amino]-3-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]propyl]phenyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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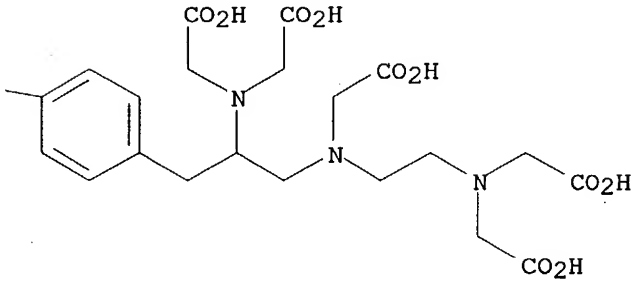


L9 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:39624 HCAPLUS
DOCUMENT NUMBER:	139:210070
TITLE:	Improved Iodine Radiolabels for Monoclonal Antibody Therapy
AUTHOR(S):	Stein, Rhona; Govindan, Serengulam V.; Mattes, M. Jules; Chen, Susan; Reed, Linda; Newsome, Guy; McBride, Bill J.; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE:	Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE:	Cancer Research (2003), 63(1), 111-118

Searcher : Shears 571-272-2528

CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A major disadvantage of 131iodine (I)-labeled monoclonal antibodies (MAbs) for radioimmunotherapy has been the rapid diffusion of iodotyrosine from target cells after internalization and catabolism of the radioiodinated MAbs. We recently reported that a radioiodinated, diethylenetriaminepentaacetic acid-appended peptide, designated immunomedics' residualizing peptide 1 (IMP-R1), was a residualizing iodine label that overcame many of the limitations that had impeded the development of residualizing iodine for clin. use. To determine the factors governing the therapeutic index of the labeled MAb, as well as the factors required for production of radioiodinated MAb in high yield and with high specific activity, variations in the peptide structure of IMP-R1 were evaluated. A series of radioiodinated, diethylenetriaminepentaacetic acid-appended peptide moieties (IMP-R1 through IMP-R8) that differed in overall hydrophilicity and charge were compared. Radioiodinations of the peptides followed by conjugations to disulfide-reduced RS7 (an anti-epithelial glycoprotein-1 MAb) furnished radioimmunoconjugates in good overall incorporations, with immunoreactivities comparable to that of directly radioiodinated RS7. Specific activities of up to 8 mCi/mg and yields > 80% have been achieved. In vitro processing expts. showed marked increases in radioiodine retention with all of the adducts; radioiodine retention at 45 h was up to 86% greater in cells than with directly iodinated RS7. Each of the 125I-peptide-RS7 conjugates was compared with 131I-RS7 (labeled by the chloramine-T method) in paired-label biodistribution studies in nude mice bearing human lung tumor xenografts. All of the residualizing substrates exhibited significantly enhanced retention in tumor in comparison to directly radioiodinated RS7, but the nontarget uptakes differed significantly among the residualizing labels. The best labels were IMP-R4 and IMP-R8, showing superior tumor-to-non-tumor ratios by virtue of high tumor uptake and retention and low normal organ uptake, as well as superior radiochem. properties. The therapeutic efficacy of 131I-IMP-R4-RS7 was compared with that of conventionally 131I-labeled RS7 and 90yttrium-RS7 in the nude mice lung cancer model. The therapeutic efficacy of 131I-IMP-R4-RS7 and 90yttrium-RS7 were equivalent, and both agents yielded significantly improved control of tumor growth compared with conventional 131I-labeled RS7.

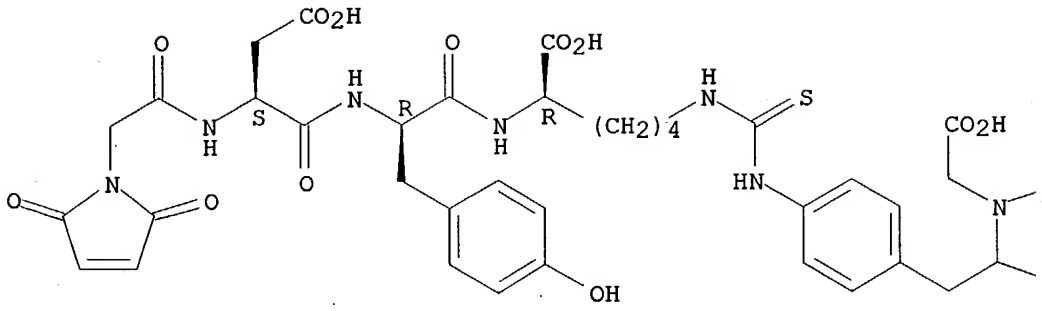
IT **588706-62-1DP**, 125I-labeled MAb conjugates
588709-17-5DP, 125I-labeled MAb conjugates
RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(125I-labeled IMP-R (immunomedics residualizing peptides)-MAb RS7 conjugates for cancer radioimmunotherapy)

RN 588706-62-1 HCAPLUS

CN D-Lysine, N-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)acetyl]-L-α-aspartyl-D-tyrosyl-N6-[[[4-[2-[bis(carboxymethyl)amino]-3-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]propyl]phenyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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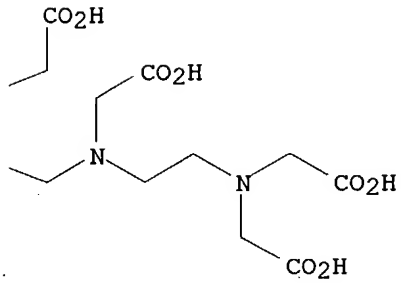

RN 588709-17-5 HCAPLUS
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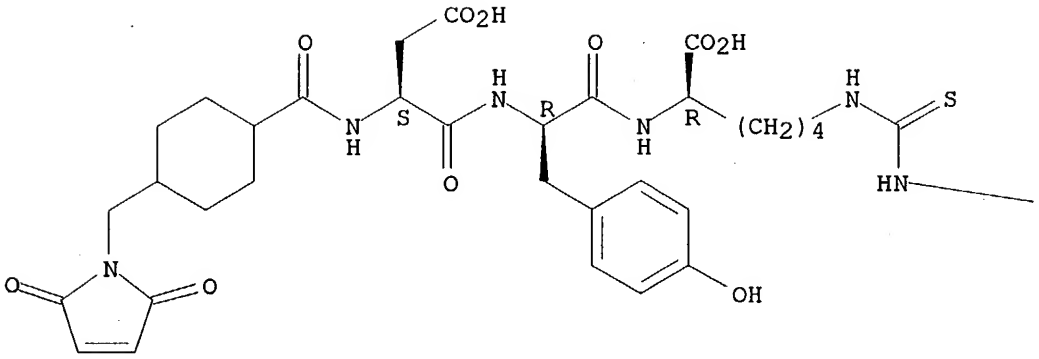
Absolute stereochemistry.

PAGE 1-A



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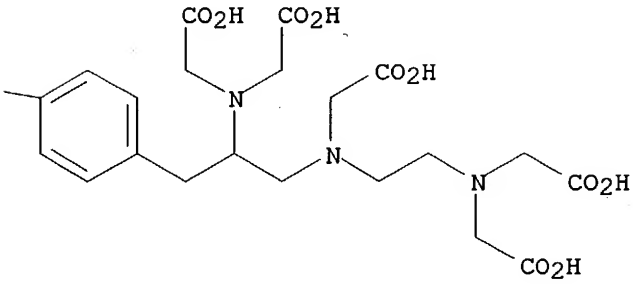


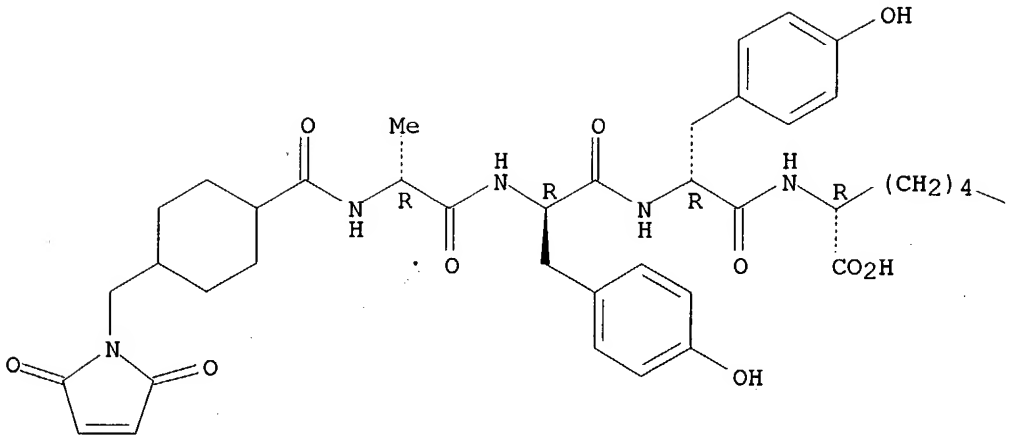
IT **224045-69-6D,** 125I-labeled MAb conjugates
261516-54-5D, 125I-labeled MAb conjugates
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(125I-labeled IMP-R (immunomedics residualizing peptides)-MAb RS7 conjugates for cancer radioimmunotherapy)

RN 224045-69-6 HCAPLUS

CN D-Lysine, 1',1'''-[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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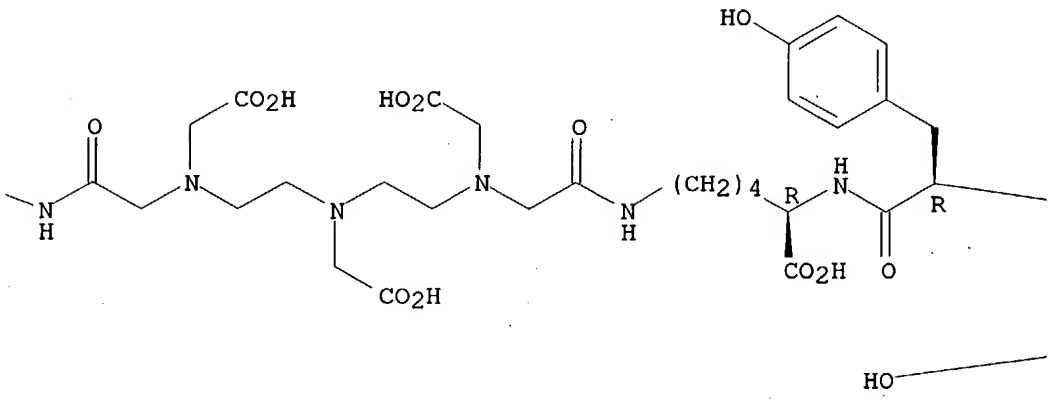

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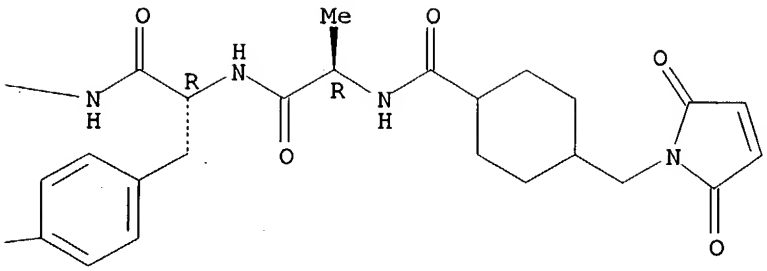

RN 261516-54-5 HCAPLUS
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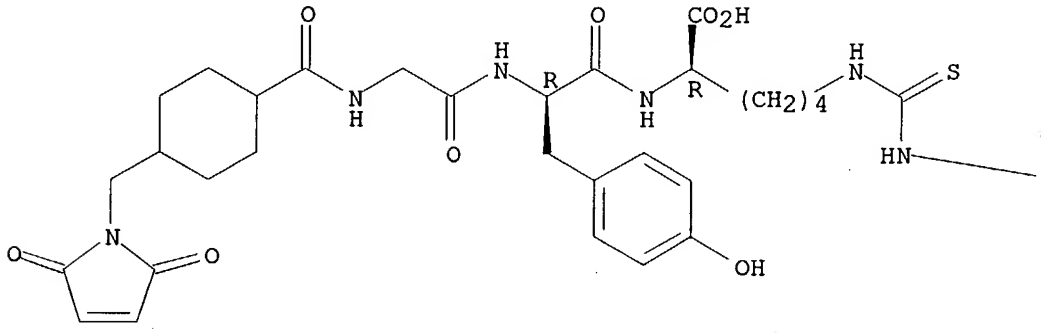
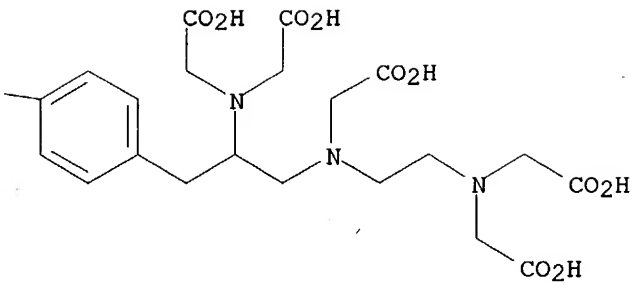
Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:697382 HCAPLUS
DOCUMENT NUMBER: 136:275439
TITLE: Radioimmunotherapy of a human lung cancer xenograft with monoclonal antibody RS7: Evaluation of 177Lu and comparison of its efficacy with that of 90Y and residualizing 131I
AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.; Chen, Susan; Reed, Linda; Richel, Heidi; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE: Journal of Nuclear Medicine (2001), 42(6), 967-974
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor targeting and therapeutic efficacy of 177Lu-labeled monoclonal antibody (mAb) RS7 (antiepithelial glycoprotein-1) was evaluated in a human nonsmall cell lung carcinoma xenograft model. The potential of 177Lu-labeled RS7 was compared with that of RS7 labeled with 90Y and a residualizing form of 131I. A 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA) conjugate of RS7 was used for radiolabeling with 177Lu-acetate or 88/90Y-acetate. Biodistribution and therapy studies were conducted in nude mice with s.c. Calu-3 xenografts. Therapy studies were performed using the maximal tolerated doses (MTDs) of 90Y-DOTA-RS7 (3.9 MBq [105 ≥Ci]) and 177Lu-DOTA-RS7 (10.2 MBq [275 ≥Ci]) and compared with the data obtained using the MTD (13.0 MBq [350 μCi]) of a residualizing form of 131I-RS7. Radiolabeling of RS7-DOTA conjugate with 177Lu-acetate was facile. 177Lu-DOTA-RS7 displayed biodistribution results that were nearly identical to that of the 88Y analog in a paired-label study. The mean percentage injected doses per g (%ID/g) for 177Lu-RS7 and 88Y-RS7 (in parentheses) in

tumor were 38.3 %ID/g (39.1 %ID/g), 63.0 %ID/g (66.0 %ID/g), 63.0 %ID/g (65.8 %ID/g), and 34.0 %ID/g (34.9 %ID/g) on days 1, 3, 7, and 14, resp. Elimination of established tumors, with an initial mean tumor volume of 0.24 cm3, was shown using doses of 177Lu-DOTA-RS7 ranging from 5.6 to 9.3 MBq (150-250 μCi) per nude mouse, with no significant difference in response rate noted between the doses in this range. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, in which 177Lu-DOTA-RS7 was markedly more effective than the 177Lu-DOTA control antibody. A comparison of the therapeutic efficacies of 177Lu-DOTA-RS7 and 90Y-DOTA-RS7, using mice with established tumors with an initial mean tumor volume of 0.85 cm3, indicated similar tumor growth inhibition and similar tumor regrowth profiles. The therapy data were similar to those obtained with residualizing 131I-RS7 obtained at the same time. 177Lu-RS7 is an effective radioimmunoconjugate for radioimmunotherapy. With its radiophys. properties similar to those of 131I, coupled with its facile and stable attachment to mAb, 177Lu promises to be an alternative to 131I, and a complement to 90Y, in radioimmunotherapy.

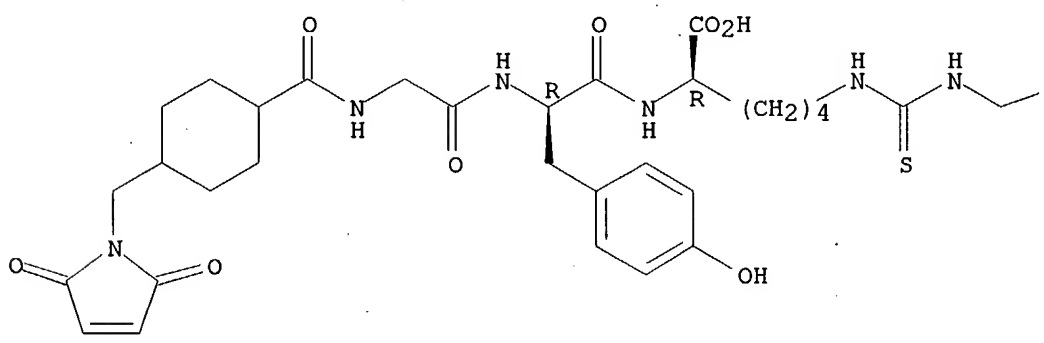
IT **224045-67-4D**, IMP-R 1, 131I-labeled antibody conjugate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radioimmunotherapy of lung cancer with 177Lu-labeled monoclonal antibody RS7: comparison with 90Y and residualizing 131I)

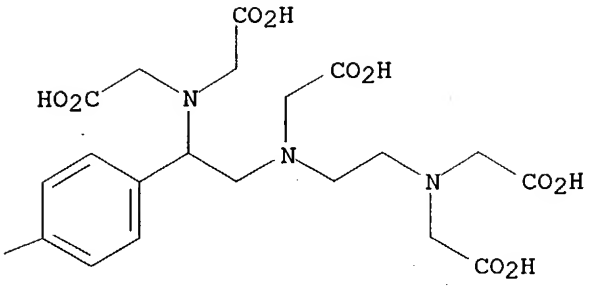
RN 224045-67-4 HCAPLUS

CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[[[[4-[1-[bis(carboxymethyl)amino]-2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]phenyl]methyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:740238 HCAPLUS
DOCUMENT NUMBER: 132:218942
TITLE: Targeting human cancer xenografts with monoclonal antibodies labeled using radioiodinated, diethylenetriaminepentaacetic acid-appended peptides
AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.; Jules, Mattes, M.; Shih, Lisa B.; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE: Clinical Cancer Research (1999), 5(10, Suppl.), 3079s-3087s
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new nonmetabolizable peptide approach to the production of residualizing radioiodine was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were radioiodinated using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, 111In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per g of tissue in Calu-3 was 7.9 ± 4.1% and 18.1 ± 7.9% ($P < 0.05$) for the conventional 131I- and 125I-IMP-R1-RS7, resp., and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also

improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when 125I-IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing radioiodine label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in radioiodine incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

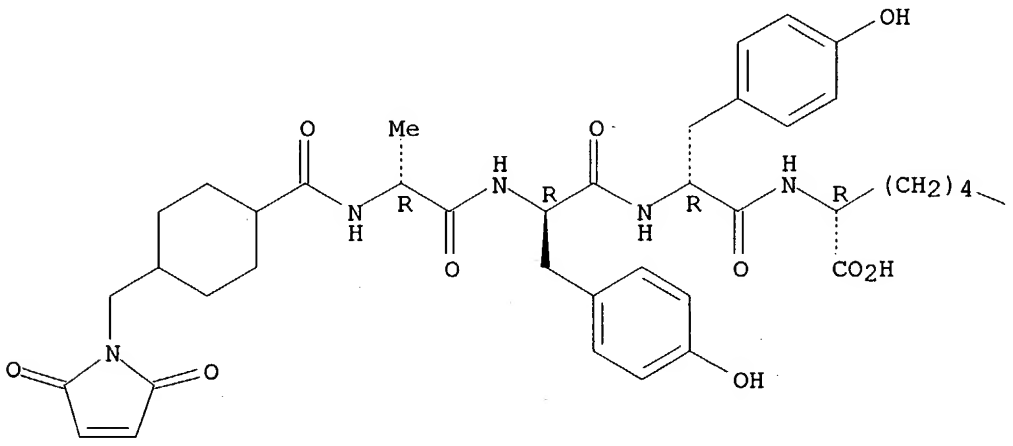
IT **224045-69-6D**, radiolabeled monoclonal antibody conjugates
261516-54-5D, radiolabeled monoclonal antibody conjugates
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(targeting human cancer xenografts with monoclonal antibodies labeled using radioiodinated, diethylenetriaminepentaacetic acid-appended peptides)

RN 224045-69-6 HCAPLUS

CN D-Lysine, 1',1'''-[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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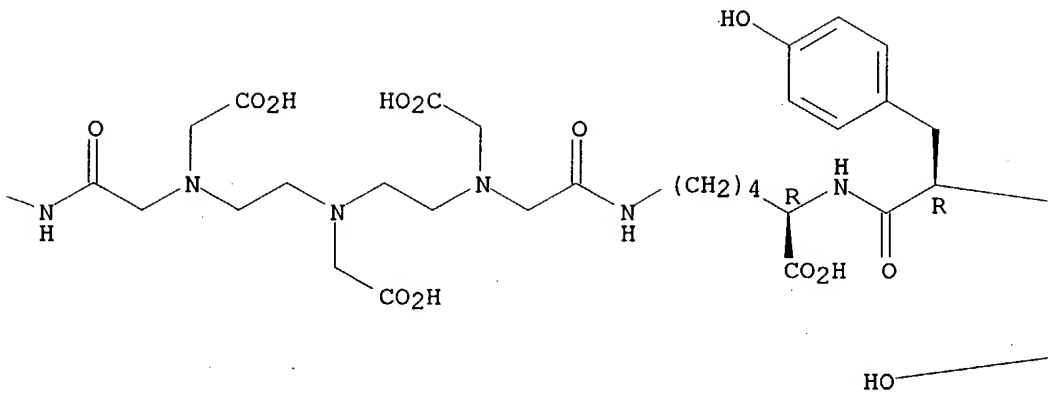

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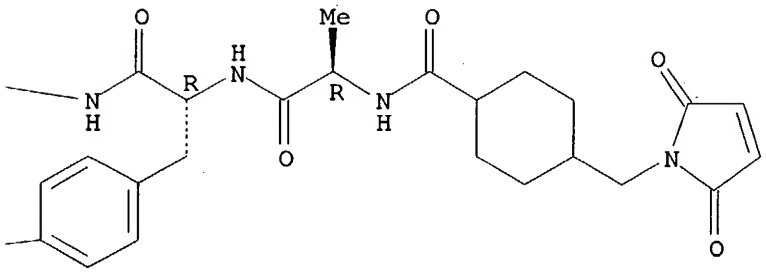
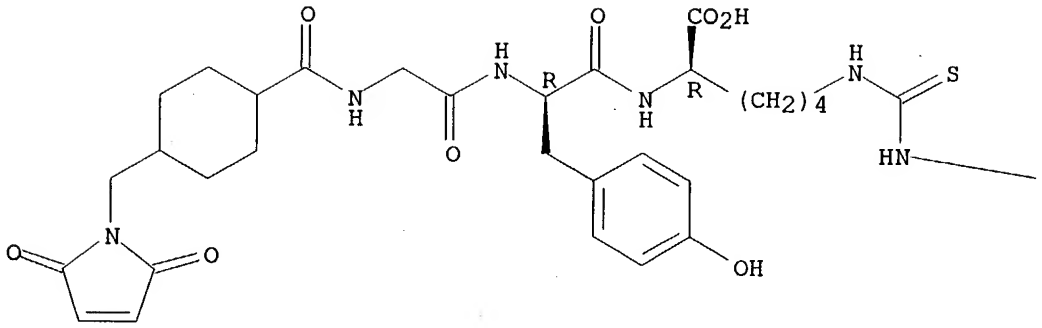


RN 261516-54-5 HCAPLUS
CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[[[4-[2-[bis(carboxymethyl)amino]-3-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]propyl]phenyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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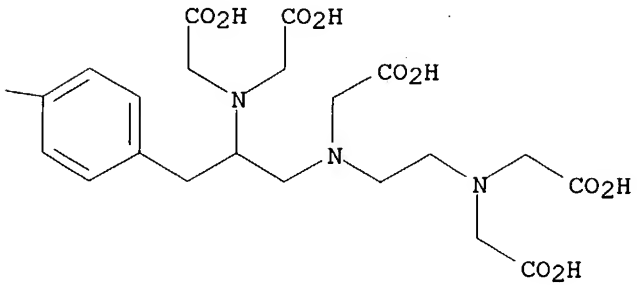


REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:402525 HCAPLUS
DOCUMENT NUMBER: 131:211044
TITLE: Cytotoxicity with Auger electron-emitting radionuclides delivered by antibodies
AUTHOR(S): Grifiths, Gary L.; Govindan, Serengulam V.; Sgouros, George; Ong, Gaik Lin; Goldenberg, David M.; Mattes, M. Jules
CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, USA
SOURCE: International Journal of Cancer (1999), 81(6), 985-992
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the in vitro cytotoxic potential of Auger electron-emitting radionuclides delivered to the cytoplasm or, more

specifically, to lysosomes, via antibodies. The antibody (Ab) used was LLI, which is specific for CD74, an epitope of the major histocompatibility complex (MHC) class II antigen invariant chain, II, present on the cell surface. It is taken up in large amts., approx. 107 Ab mols. per cell per day, and delivered to lysosomes. The radioisotopes tested included 111In, 99mTc and 125I. With sufficient specific activity, approx. 10 mCi/mg Ab, all of these isotopes were potent cytotoxic agents. 125I was active only if a "residualizing" form was used, meaning a form that is trapped within cells after catabolism of the Ab to which it was conjugated (conventional oxidative iodination produces a non-residualizing label). The conjugates of 111In and 99mTc used are known to be residualizing. One hundred percent cell kill in vitro was obtained with 111In and 125I, under conditions in which a non-reactive control Ab, conjugated in the same way, produced no significant toxicity. 99mTc was also potent and specific, but appeared somewhat less active than the other isotopes under the conditions evaluated. Although few Abs are accreted by cells at the same rate as LLI, it may be possible to use other Abs to deliver similar amts. of radioactivity, if Abs with higher specific activity can be produced. Such conjugated radioisotopes may be useful for attacking tumor cells in vivo, particularly for single cells or micrometastases.

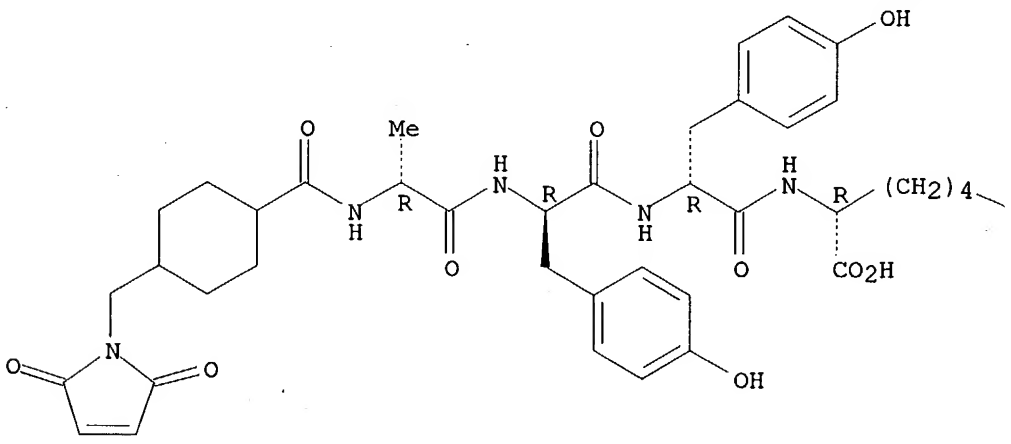
IT **224045-69-6D**, radiolabeled antibody conjugates
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cytotoxicity with Auger electron-emitting radionuclides delivered by antibodies)

RN 224045-69-6 HCAPLUS

CN D-Lysine, 1',1'''-[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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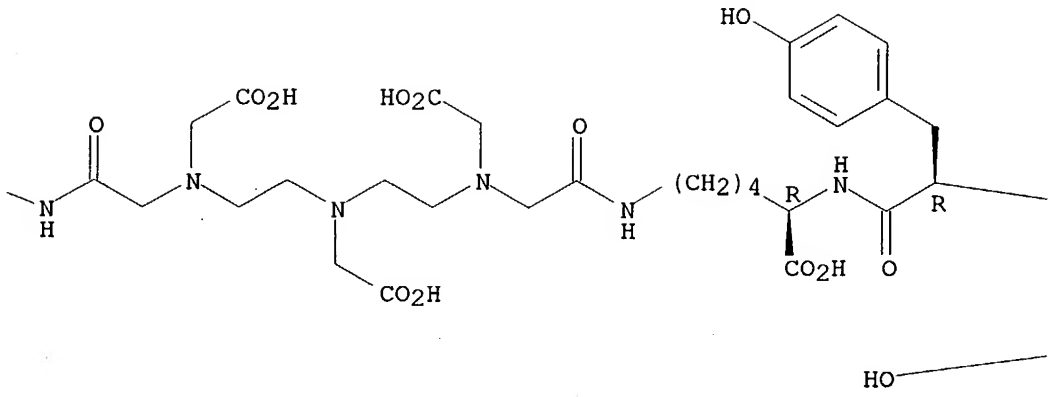
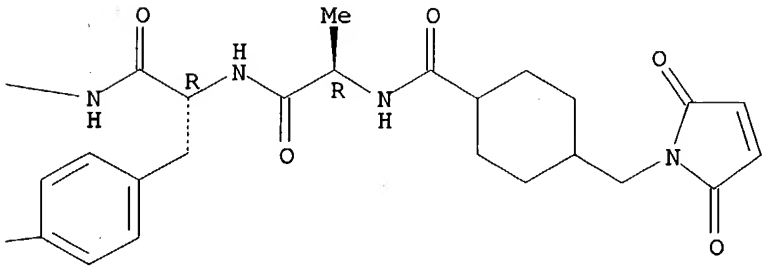


PAGE 1-C



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:90010 HCAPLUS
DOCUMENT NUMBER: 130:334689
TITLE: Labeling of Monoclonal Antibodies with Diethylenetriaminepentaacetic Acid-Appended Radioiodinated Peptides Containing D-Amino Acids
AUTHOR(S): Govindan, Serengulam V.; Mattes, M. Jules; Stein, Rhona; McBride, Bill J.; Karacay, Habibe; Goldenberg, David M.; Hansen, Hans J.; Griffiths, Gary L.
CORPORATE SOURCE: Immunomedics Inc., Morris Plains, NJ, 07950, USA
SOURCE: Bioconjugate Chemistry (1999), 10(2), 231-240

Searcher : Shears 571-272-2528

CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The optimal use of radioiodinated internalizing monoclonal antibodies (mAbs) for radio-immunotherapy necessitates the development of practical methods for increasing the level of retention of 131I in the tumor. Lysosomally trapped ("residualizing") iodine radiolabels that have been previously designed are based mostly on carbohydrate-tyramine adducts, but these methods have drawbacks of low overall yields and/or high levels of mAb aggregation. We have developed a method using thiol-reactive diethylenetriaminepentaacetic acid (DTPA)-peptide adducts wherein the peptides are assembled with one or more D-amino acids, including D-tyrosine. Two such substrates, R-Gly-D-Tyr-D-Lys[1-(p-thiocarbonylaminobenzyl)DTPA], referred to as IMP-R1, and [R-D-Ala-D-Tyr-D-Tyr-D-Lys]2(CA-DTPA), referred to as IMP-R2, wherein R is 4-(N-maleimidomethyl)cyclohexane-1-carbonyl, were synthesized by preparing functional group-protected peptides on a solid phase, selectively derivatizing the lysine side chain with 1-(p-isothiocyanatobenzyl)DTPA or DTPA dianhydride (CA-DTPA), deprotecting other functional groups, and finally derivatizing the peptide's N-terminus so it contained a maleimide group. Radioiodinations of the peptides followed by conjugations to disulfide-reduced mAbs, carried out as a one-vial procedure, resulted in 32-89% overall yields, at specific activities of 1.8-11.1 mCi/mg, with less than 2% aggregation. Two internalizing mAbs, LL2 (anti-CD 22 B-cell lymphoma mAb) and RS7 (an anti-adenocarcinoma mAb which targets EGP-1 antigen), labeled with this procedure exhibited a 2-3-fold better cellular retention in Ramos and Calu-3 tumor cell lines, in vitro, resp., compared to the same mAbs radioiodinated with the chloramine-T method. The rationale for the new approach, syntheses, radiochem. and in vitro data are presented.

IT **224045-67-4P 224045-69-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; labeling of monoclonal antibodies with DTPA-appended radioiodinated peptides containing D-amino acids and tumor cell uptake)

RN 224045-67-4 HCAPLUS

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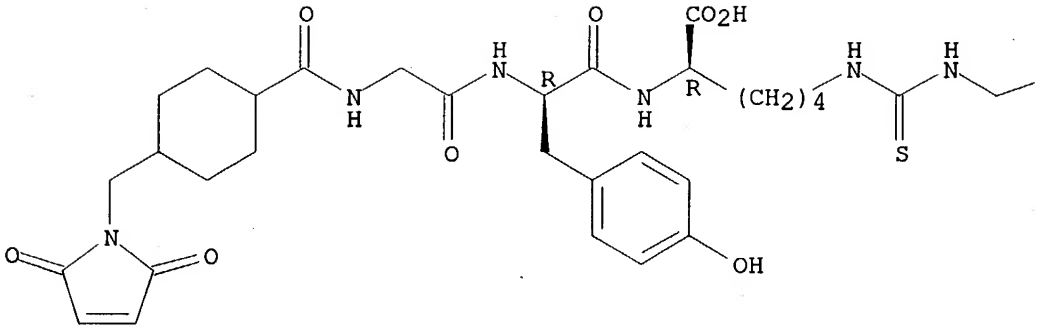
Absolute stereochemistry.

PAGE 1-A



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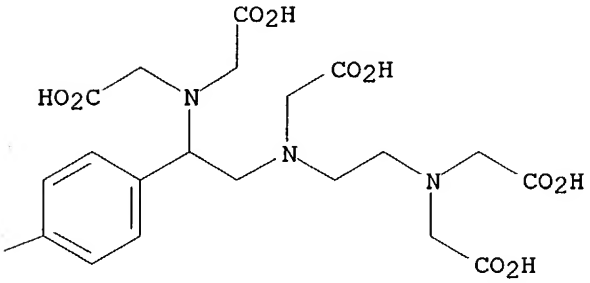

RN 224045-69-6 HCAPLUS
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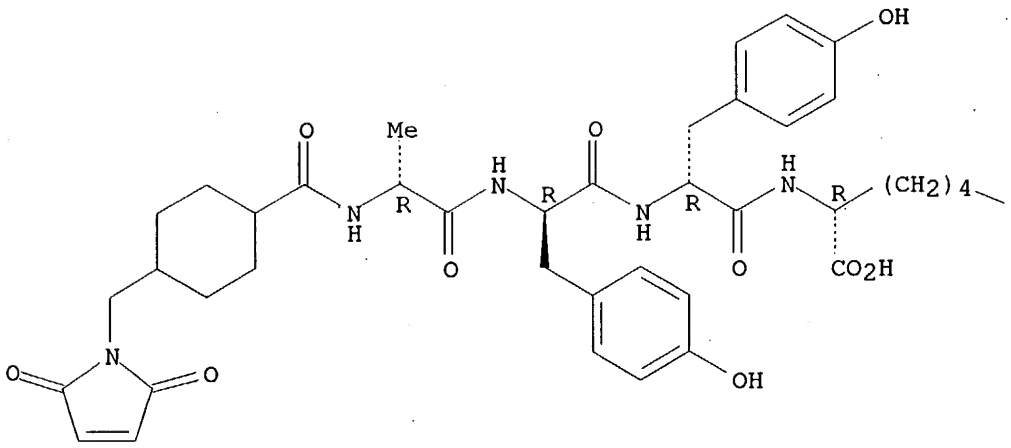
Absolute stereochemistry.

PAGE 1-A



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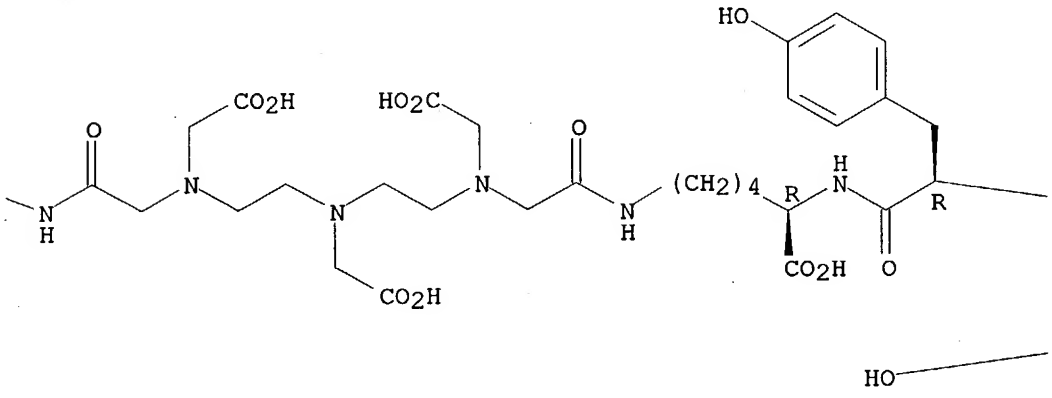

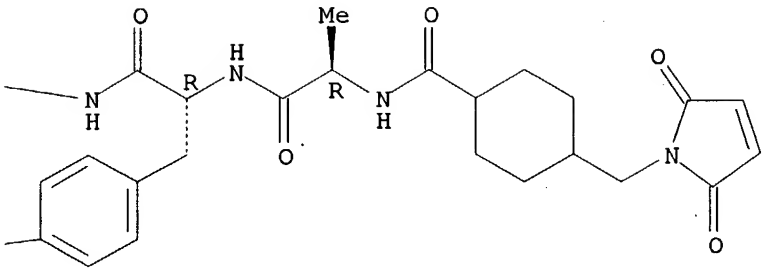

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FILE 'CAOLD' ENTERED AT 09:36:32 ON 15 APR 2004
L10 0 S L8

FILE 'USPATFULL' ENTERED AT 09:36:42 ON 15 APR 2004
L11 2 S L8

L11 ANSWER 1 OF 2 USPATFULL on STN
ACCESSION NUMBER: 2004:1806 USPATFULL
TITLE: RS7 antibodies
INVENTOR(S): Govindan, Serengulam, Summit, NJ, UNITED STATES
Qu, Zhengxing, Warren, NJ, UNITED STATES
Hansen, Hans, Picayune, MS, UNITED STATES
Goldenberg, David, Mendham, NJ, UNITED STATES
PATENT ASSIGNEE(S): Immunomedics, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004001825	A1	20040101
APPLICATION INFO.:	US 2003-377121	A1	20030303 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-360229P	20020301 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 3417
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to monovalent and multivalent, monospecific binding proteins and to multivalent, multispecific binding

proteins. One embodiment of these binding proteins has one or more binding sites where each binding site binds with a target antigen or an epitope on a target antigen. Another embodiment of these binding proteins has two or more binding sites where each binding site has affinity towards different epitopes on a target antigen or has affinity towards either a target antigen or a hapten. The present invention further relates to recombinant vectors useful for the expression of these functional binding proteins in a host. More specifically, the present invention relates to the tumor-associated antigen binding protein designated RS7, and other EGP-1 binding-proteins. The invention further relates to humanized, human and chimeric RS7 antigen binding proteins, and the use of such binding proteins in diagnosis and therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER:	2003:326858 USPATFULL
TITLE:	Stable radioiodine conjugates and methods for their synthesis
INVENTOR(S):	Govindan, Serengulam V., Summit, NJ, United States
PATENT ASSIGNEE(S):	Immunomedics, Inc., Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6663866	B1	20031216
APPLICATION INFO.:	US 2000-605873		20000629 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-919477, filed on 28 Aug 1997, now patented, Pat. No. US 6558669		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-24738P	19960828 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Celsa, Bennett
LEGAL REPRESENTATIVE:	Foley & Lardner
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	1180

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

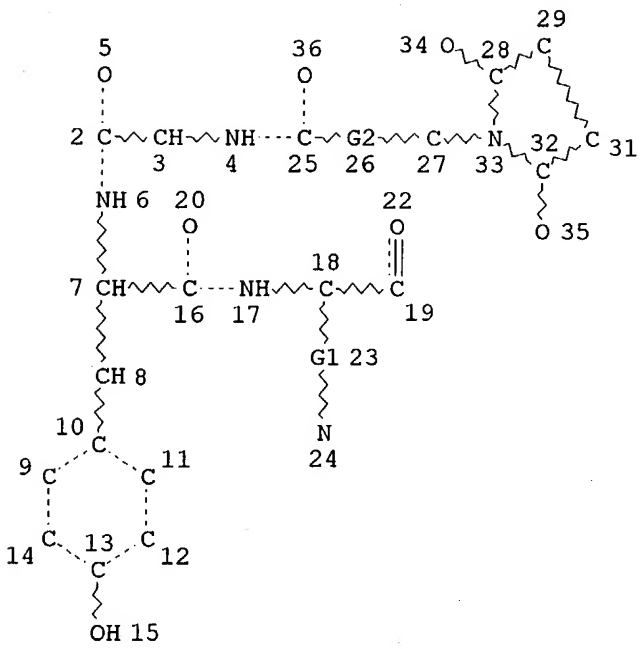
AB Methods are described for conjugating radioiodinated peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. Radioiodinated residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant radioiodinated residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

(FILE 'MARPAT' ENTERED AT 09:37:07 ON 15 APR 2004)

Searcher : Shears 571-272-2528

L4 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
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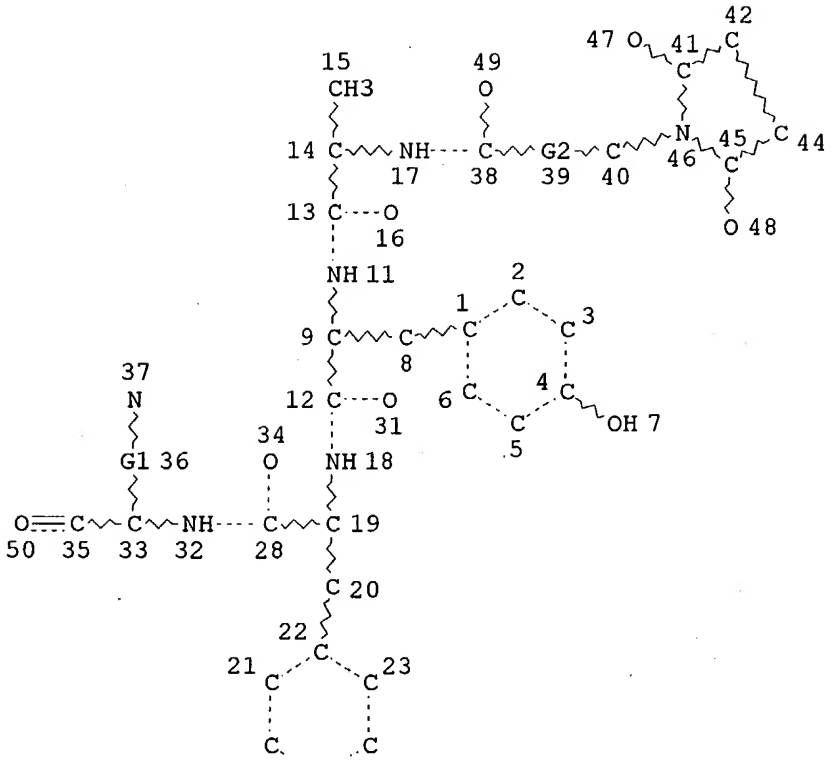

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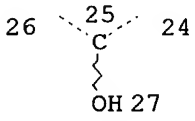

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STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
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L14 0 SEA FILE=MARPAT SSS FUL L6 (MODIFIED ATTRIBUTES)

100.0% PROCESSED 2931 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.18

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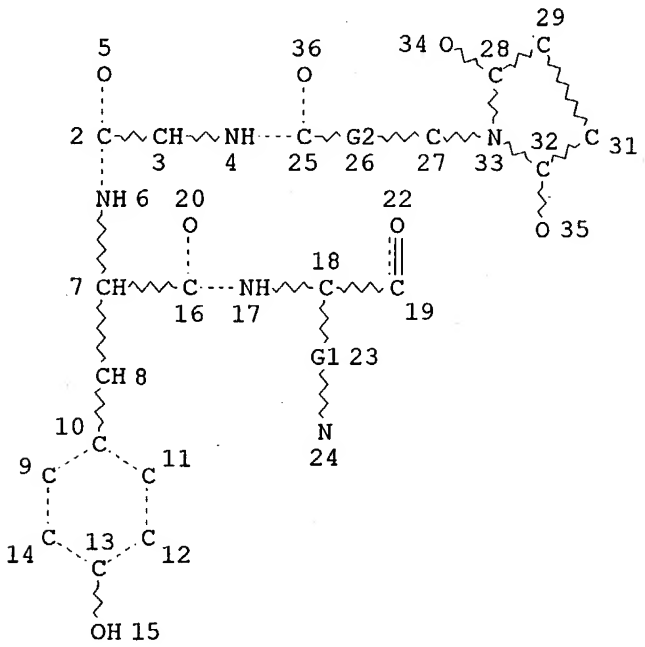

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REP G2=(0-1) CB
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 33

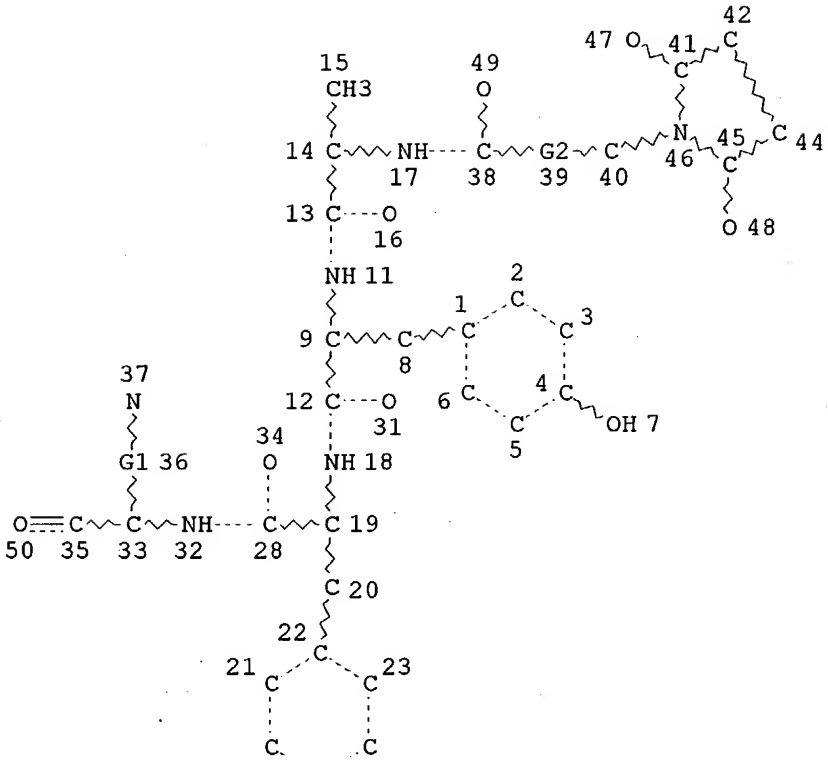
STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

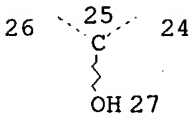
L15 0 SEA FILE=MARPATPREV SSS FUL L4 (MODIFIED ATTRIBUTES)

100.0% PROCESSED 5 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L6 STR



Page 1-A



Page 2-A
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REP G2=(0-1) CB
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 46

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L16 0 SEA FILE=MARPATPREV SSS FUL L6 (MODIFIED ATTRIBUTES)

Searcher : Shears 571-272-2528

100.0% PROCESSED 5 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, DISSABS, CANCERLIT' ENTERED AT 09:40:25 ON 15 APR 2004)

- Author (s)

L17 361 S "GOVINDAN S"?/AU
L18 3197 S "GRIFFITHS G"?/AU
L19 160 S L17 AND L18
L20 3398 S L17 OR L18
L21 73 S (L19 OR L20) AND (RADIOIODIN? OR RADIO IODIN?)
L22 29 DUP REM L21 (44 DUPLICATES REMOVED)
L23 234 S RADIO I
L24 0 S (L19 OR L20) AND L23

L22 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:175088 HCAPLUS
TITLE: Preclinical Therapy of Breast Cancer with a **Radioiodinated** Humanized Anti-EGP-1 Monoclonal Antibody: Advantage of a Residualizing Iodine Radiolabel
AUTHOR(S): **Govindan, Serengulam V.**; Stein, Rhona; Qu, Zhengxing; Chen, Susan; Andrews, Philip; Ma, Hong; Hansen, Hans J.; **Griffiths, Gary L.**; Horak, Ivan D.; Goldenberg, David M.
CORPORATE SOURCE: Immunomedics, Inc.
SOURCE: Breast Cancer Research and Treatment (2004), 84(2), 173-182
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background. A humanized monoclonal antibody (MAb), hRS7, labeled with 131I-IMP-R4, was evaluated for the preclin. radioimmunotherapy (RAIT) of breast cancer. 131I-IMP-R4 is an improved residualizing form of 131I that overcomes the short tumor residence time associated with conventionally **radioiodinated** MAbs. RS7, an internalizing MAb, recognizes epithelial glycoprotein-1, which is highly expressed in the carcinomas of breast, lung, ovary, and prostate. Methods. A humanized version of RS7 was generated by CDR-grafting and transfection. In vivo expts. were carried out in nude mice bearing s.c. MDA-MB-468 human breast cancer xenografts. Therapy expts. were performed using established tumors with mean tumor volume (MTV) of 0.3 cm3, and single administrations, at .apprx.70% of the estimated maximum tolerated doses (MTD), of the residualizing 131I-IMP-R4-hRS7 and 131I-hRS7 prepared by the conventional chloramine-T method [131I-hRS7 (CT)]. Therapeutic specificity was determined by comparison with untreated and non-specific MAb controls. Results. hRS7 was functionally very similar to murine and chimeric RS7. A biodistribution study using 125I-IMP-R4-hRS7 and 131I-hRS7 (CT) indicated a dosimetric advantage for the former. The MTVs 8 wk post-treatment were 20, 163, and 280% of the starting MTVs of 131I-IMP-R4-hRS7-treated, 131I-hRS7 (CT)-treated, and untreated groups, resp. Complete remissions were seen in 5 of 11 [and 6 of 8] mice treated with 131I-IMP-R4-hRS7, and in 1 of 11 mice treated with 131I-hRS7(CT). 131I-IMP-R4-hRS7 was significantly more

efficacious than 131I-hRS7 (CT) [P = 0.01 for AUC] and the control 131I-IMP-R4-MAb. Conclusion. 131I-IMP-R4-hRS7 is a promising new agent for RAIT, providing significant therapeutic advantage in comparison to the conventionally 131I-labeled antibody.

L22 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:980784 HCAPLUS
DOCUMENT NUMBER: 140:47476
TITLE: Stable **radioiodine** conjugates and methods for their synthesis
INVENTOR(S): **Govindan, Serengulam V.**
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,558,669. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6663866	B1	20031216	US 2000-605873	20000629
US 6558669	B1	20030506	US 1997-919477	19970828
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1299129	A2	20030409	EP 2001-950673	20010629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003220470	A1	20031127	US 2003-359276	20030206
US 2004018148	A1	20040129	US 2003-395718	20030325
US 2004022725	A1	20040205	US 2003-411370	20030411

PRIORITY APPLN. INFO.:

US 1996-24738P	P	19960828
US 1997-919477	A2	19970828
WO 1997-US14998	A	19970827
EP 1997-954212	A3	19971219
WO 1997-US23711	A	19971219
US 2000-605873	A	20000629
US 2000-696740	A2	20001026
WO 2001-US20764	W	20010629

APPL.

AB Methods are described for conjugating **radioiodinated** peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. **Radioiodinated** residualizing

antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant **radioiodinated** residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy of tumors.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:931008 HCAPLUS
DOCUMENT NUMBER: 140:8761
TITLE: Methods for the purification of stable **radioiodine** conjugates
INVENTOR(S): **Govindan, Sergenulam V.**
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 696,740.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003220470	A1	20031127	US 2003-359276	20030206
WO 9808548	A2	19980305	WO 1997-US14998	19970827
WO 9808548	A3	19980423		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6558669	B1	20030506	US 1997-919477	19970828
WO 9911294	A1	19990311	WO 1997-US23711	19971219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6663866	B1	20031216	US 2000-605873	20000629

PRIORITY APPLN. INFO.:

US 1996-24738P	P	19960828
WO 1997-US14998	A	19970827
US 1997-919477	A2	19970828

Appl.

Searcher : Shears 571-272-2528

WO 1997-US23711 A 19971219
US 2000-605873 A2 20000629
US 2000-696740 A2 20001026
EP 1997-954212 A3 19971219

AB The present invention relates to the purification of reagents used in radioimmunodetection and radioimmunotherapy and specifically to the purification of **radioiodine** labeled conjugates having enhanced stability in vivo and enhanced retention at tumor sites. It is directed toward a method for preparing and purifying a conjugate of a **radioiodinated** aminopolycarboxylate-appended peptide and a targeting agent. The method involves (A) providing a solution comprising (i) unbound **radioiodine** (ii) a **radioiodinated** aminopolycarboxylate-appended peptide that is not conjugated to a targeting agent (iii) and a **radioiodinated** aminopolycarboxylate-appended peptide that is conjugated to the targeting agent; (B) contacting the solution with an anion-exchange resin; and (C) passing the anion-exchange resin and solution together through a filter capable of trapping anion-exchange resin particles.

L22 ANSWER 4 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:265963 BIOSIS
DOCUMENT NUMBER: PREV200300265963
TITLE: Stable **radioiodine** conjugates and methods for their synthesis.
AUTHOR(S): **Govindan, Serengulam V.** [Inventor, Reprint Author]; **Griffiths, Gary L.** [Inventor]
CORPORATE SOURCE: ASSIGNEE: Immunomedics, Inc.
PATENT INFORMATION: US 6558669 May 06, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 6 2003) Vol. 1270, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jun 2003
Last Updated on STN: 4 Jun 2003

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable amide bonds are coupled to antibodies. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to antibodies. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to antibodies. In a fourth method, a hydrazide-appended antibody is coupled to a **radioiodinated** carbohydrate or a thiolated antibody is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method a monoderivatized cyanuric chloride is used to conjugate thiolated antibody. **Radioiodinated** residualizing antibody conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

L22 ANSWER 5 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2004:51001 SCISEARCH
THE GENUINE ARTICLE: 756LU
TITLE: Residualizing **radioiodine**-labeled MAbs for therapy of colon cancer: A new radioimmunotherapeutic.
AUTHOR: Stein R (Reprint); Von Govindan S; Chen S; Rosario A; Andrews P; **Griffiths G**; Hansen H J; Horak I D; Goldenberg D M
CORPORATE SOURCE: Garden State Canc Ctr, Belleville, NJ USA; Immunomed Inc, Morris Plains, NJ USA
COUNTRY OF AUTHOR: USA
SOURCE: CLINICAL CANCER RESEARCH, (1 DEC 2003) Vol. 9, No. 16, Part 2, Supp. [S], pp. 6190S-6191S. Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA. ISSN: 1078-0432.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L22 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:39624 HCAPLUS
DOCUMENT NUMBER: 139:210070
TITLE: Improved Iodine Radiolabels for Monoclonal Antibody Therapy
AUTHOR(S): Stein, Rhona; **Govindan, Serengulam V.**; Mattes, M. Jules; Chen, Susan; Reed, Linda; Newsome, Guy; McBride, Bill J.; **Griffiths, Gary L.**; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE: Cancer Research (2003), 63(1), 111-118 CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A major disadvantage of 131iodine (I)-labeled monoclonal antibodies (MAbs) for radioimmunotherapy has been the rapid diffusion of iodotyrosine from target cells after internalization and catabolism of the **radioiodinated** MAbs. We recently reported that a **radioiodinated**, diethylenetriaminepentaacetic acid-appended peptide, designated immunomedics' residualizing peptide 1 (IMP-R1), was a residualizing iodine label that overcame many of the limitations that had impeded the development of residualizing iodine for clin. use. To determine the factors governing the therapeutic index of the labeled MAb, as well as the factors required for production of **radioiodinated** MAb in high yield and with high specific activity, variations in the peptide structure of IMP-R1 were evaluated. A series of **radioiodinated**, diethylenetriaminepentaacetic acid-appended peptide moieties (IMP-R1 through IMP-R8) that differed in overall hydrophilicity and charge were compared. **Radioiodinations** of the peptides followed by conjugations to disulfide-reduced RS7 (an anti-epithelial

glycoprotein-1 MAb) furnished radioimmunoconjugates in good overall incorporations, with immunoreactivities comparable to that of directly **radioiodinated** RS7. Specific activities of up to 8 mCi/mg and yields > 80% have been achieved. In vitro processing expts. showed marked increases in **radioiodine** retention with all of the adducts; **radioiodine** retention at 45 h was up to 86% greater in cells than with directly iodinated RS7. Each of the 125I-peptide-RS7 conjugates was compared with 131I-RS7 (labeled by the chloramine-T method) in paired-label biodistribution studies in nude mice bearing human lung tumor xenografts. All of the residualizing substrates exhibited significantly enhanced retention in tumor in comparison to directly **radioiodinated** RS7, but the nontarget uptakes differed significantly among the residualizing labels. The best labels were IMP-R4 and IMP-R8, showing superior tumor-to-non-tumor ratios by virtue of high tumor uptake and retention and low normal organ uptake, as well as superior radiochem. properties. The therapeutic efficacy of 131I-IMP-R4-RS7 was compared with that of conventionally 131I-labeled RS7 and 90yttrium-RS7 in the nude mice lung cancer model. The therapeutic efficacy of 131I-IMP-R4-RS7 and 90yttrium-RS7 were equivalent, and both agents yielded significantly improved control of tumor growth compared with conventional 131I-labeled RS7.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 7 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:370786 BIOSIS
DOCUMENT NUMBER: PREV200300370786
TITLE: A simplified one-pot preparation and purification method for labeling an anti-CEA MAB, hMN-14, with a residualizing form of 131I.
AUTHOR(S): **Govindan, S. V.** [Reprint Author]; **Griffiths, G. L.**; Andrews, P.; Hansen, H. J.; Horak, I.; Goldenberg, D. M.
CORPORATE SOURCE: Research, Immunomedics, Inc., Morris Plains, NJ, USA
SOURCE: Journal of Nuclear Medicine, (May 2003) Vol. 44, No. 5 Supplement, pp. 100P. print.
Meeting Info.: 50th Annual Meeting of the Society of Nuclear Medicine. New Orleans, LA, USA. June 21-25, 2003. Society of Nuclear Medicine.
ISSN: 0161-5505 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003

L22 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2002:31289 HCAPLUS
DOCUMENT NUMBER: 136:107479
TITLE: Stable **radioiodine** conjugates and methods for their synthesis
INVENTOR(S): **Govindan, Serengulam V.**

Searcher : Shears 571-272-2528

PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6663866	B1	20031216	US 2000-605873	20000629
EP 1299129	A2	20030409	EP 2001-950673	20010629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:

US 2000-605873	A	20000629
US 1996-24738P	P	19960828
US 1997-919477	A2	19970828
WO 2001-US20764	W	20010629

APPL.

AB Methods are described for conjugating **radioiodinated** peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. **Radioiodinated** residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant **radioiodinated** residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

L22 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:306823 HCAPLUS
DOCUMENT NUMBER: 139:334838
TITLE: Radiolabeled conjugates for direct and pretargeted radioimmunotherapy
AUTHOR(S): **Govindan, S. V.; Griffiths, G. L.**; Hansen, H. J.; Goldenberg, D. M.
CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SOURCE: Recent Research Developments in Bioconjugate Chemistry (2002), 1, 1-13
CODEN: RRDBEO
PUBLISHER: Transworld Research Network
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Targeted radiotherapy of cancer via tumor-specific antibodies necessitates the design of optimally performing radiolabeled conjugates whose preparation must be efficient. Very stable

radiometalations of monoclonal antibodies using simple and expeditious procedures, methods to introduce intracellularly-stable **radioiodine**, and the syntheses of special low mol. mass haptens for pretargeting strategies are some of the recent advances made in this regard. These current trends in radiolabeling chemistries of bioconjugates are illustrated with examples taken from research at the authors' institutions.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 10 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:485438 SCISEARCH
THE GENUINE ARTICLE: 439XN
TITLE: Radioimmunotherapy of a human lung cancer xenograft with monoclonal antibody RS7: Evaluation of Lu-177 and comparison of its efficacy with that of Y-90 and residualizing I-131
AUTHOR: Stein R (Reprint); **Govindan S V**; Chen S; Reed L; Richel H; **Griffiths G L**; Hansen H J; Goldenberg D M
CORPORATE SOURCE: Garden State Canc Ctr, 520 Belleville Ave, Belleville, NJ 07109 USA (Reprint); Garden State Canc Ctr, Belleville, NJ 07109 USA; Immunomed Inc, Morris Plains, NJ USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (JUN 2001) Vol. 42, No. 6, pp. 967-974.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316 USA.
ISSN: 0161-5505.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Tumor targeting and therapeutic efficacy of Lu-177-labeled monoclonal antibody (mAb) RS7 (antiepithelial glycoprotein-1) was evaluated in a human nonsmall cell lung carcinoma xenograft model. The potential of Lu-177-labeled RS7 was compared with that of RS7 labeled with Y-90 and a residualizing form of I-131. Methods: A 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA) conjugate of RS7 was used for radiolabeling with Lu-177-acetate or Y-88/90-acetate. Biodistribution and therapy studies were conducted in nude mice with subcutaneous Calu-3 xenografts. Therapy studies were performed using the maxima[tolerated doses (MTDs) of Y-90-DOTA-RS7 (3.9 MBq [105 mu Ci]) and Lu-177-DOTA-RS7 (10.2 MBq [275 mu Ci]) and compared with the data obtained using the MTD (13.0 MBq [350 mu Ci]) of a residualizing form of I-131-RS7. Results: Radiolabeling of RS7-DOTA conjugate with Lu-177-acetate was facile. Lu-177-DOTA-RS7 displayed biodistribution results that were nearly identical to that of the Y-88 analog in a paired-label study. The mean percentage injected doses per gram (%ID/g) for Lu-177-RS7 and Y-88-RS7 (in parentheses) in tumor were 38.3 %ID/g (39.1 %ID/g), 63.0 %ID/g (66.0 %ID/g), 63.0 %ID/g (65.8 %ID/ g), and 34.0 %ID/g (34.9 %ID/g) on days 1, 3, 7, and 14, respectively. Elimination of established tumors, with an initial mean tumor volume of 0.24 cm(3).

was shown using doses of Lu-177-DOTA-RS7 ranging from 5.6 to 9.3 MBq (150-250 mu Ci) per nude mouse, with no significant difference in response rate noted between the doses in this range. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, in which Lu-177-DOTA-RS7 was markedly more effective than the (LU)-L-177-DOTA control antibody. A comparison of the therapeutic efficacies of Lu-177-DOTA-RS7 and Y-90-DOTA-RS7, using mice with established tumors with an initial mean tumor volume of 0.85 cm(3), indicated similar tumor growth inhibition and similar tumor regrowth profiles. The therapy data were similar to those obtained with residualizing I-131-RS7 obtained at the same time. Conclusion: Lu-177-RS7 is an effective radioimmunoconjugate for radioimmunotherapy. With its radiophysical properties similar to those of I-131, coupled with its facile and stable attachment to mAb, Lu-177 promises to be an alternative to I-131, and a complement to Y-90, in radioimmunotherapy.

L22 ANSWER 11 OF 29 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002022221 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11418314
TITLE: Successful therapy of a human lung cancer xenograft using MAb RS7 labeled with residualizing **radioiodine.**
AUTHOR: Stein R; **Govindan S V**; Chen S; Reed L; Spiegelman H; **Griffiths G L**; Hansen H J; Goldenberg D M
CORPORATE SOURCE: Garden State Cancer Center, 520 Belleville Avenue, Belleville, NJ 07109, USA.. rstein.gscancer@att.net
CONTRACT NUMBER: CA60039 (NCI)
CA72324 (NCI)
SOURCE: Critical reviews in oncology/hematology, (2001 Jul-Aug) 39 (1-2) 173-80.
Journal code: 8916049. ISSN: 1040-8428.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011214

AB We have recently reported that a **radioiodinated,** DTPA-appended peptide, designated IMP-R1, is a residualizing iodine label that overcomes many of the limitations that have impeded the development of residualizing iodine for clinical use. In this study the potential of 131I-IMP-R1-RS7, an internalizing anti-EGP-1 monoclonal antibody, was evaluated by performing preclinical therapy studies in nude mice bearing Calu-3 human non-small cell carcinoma of the lung xenografis. Elimination of 6 of 9 established tumors (mean tumor volume=0.3 cm(3)) was observed using a single dose of 350 microCi/mouse of 131I-IMP-R1-RS7, with all animals tolerating the dose. At the same dose and specific activity of 131I-RS7, labeled using the conventional chloramine-T method, there were four deaths, and one complete remission in nine treated mice. At the maximum tolerated dose of conventionally 131I-labeled RS7, 275 microCi, mean stable disease for approximately 5 weeks was observed,

with no complete responses. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, where 131I-IMP-R1-RS7 was markedly more effective than the (131)I-IMP-R1-labeled control antibody. These studies demonstrate that (131)I-IMP-R1-RS7 provides a therapeutic advantage in comparison to conventional 131I-labeled RS7, as predicted by the increased tumor accretion observed previously in targeting studies. A direct comparison of the maximum tolerated doses of (131)I-IMP-R1-RS7 (350 microCi) and 90Y-DOTA-RS7 (105 microCi) was performed in this tumor model using large established tumors (mean tumor volume=0.85 cm(3)). Anti-tumor efficacy and toxicity of the two treatments were comparable.

L22 ANSWER 12 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:369599 BIOSIS
DOCUMENT NUMBER: PREV200100369599
TITLE: Improved internalizing **radioiodinated** monoclonal antibodies for therapy.
AUTHOR(S): Stein, Rhona [Reprint author]; **Govindan, Serengulam V.**; Mattes, M. Jules; **Griffiths, Gary L.**; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Bellville, NJ, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 93. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002

L22 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 1999:184160 HCAPLUS
DOCUMENT NUMBER: 130:219927
TITLE: Stable **radioiodine** conjugates and methods for their synthesis
INVENTOR(S): **Govindan, Serengulam V.**; **Griffiths, Gary L.**
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911294	A1	19990311	WO 1997-US23711	19971219

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6558669	B1	20030506	US 1997-919477	19970828	
CA 2302524	AA	19990311	CA 1997-2302524	19971219	
AU 9858050	A1	19990322	AU 1998-58050	19971219	
EP 1024838	A1	20000809	EP 1997-954212	19971219	
EP 1024838	B1	20020710			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001514236	T2	20010911	JP 2000-508395	19971219	
EP 1219307	A2	20020703	EP 2002-75560	19971219	
EP 1219307	A3	20040121			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
AT 220336	E	20020715	AT 1997-954212	19971219	
ES 2178042	T3	20021216	ES 1997-954212	19971219	
US 2003220470	A1	20031127	US 2003-359276	20030206	

PRIORITY APPLN. INFO.:

US 1997-919477	A2	19970828
US 1996-24738P	P	19960828
WO 1997-US14998	A	19970827
EP 1997-954212	A3	19971219
WO 1997-US23711	W	19971219
US 2000-605873	A2	20000629
US 2000-696740	A2	20001026

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable bonds such as amide bonds are coupled to cell targeting protein. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to protein. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to protein. In a fourth method, a hydrazide-appended protein is coupled to a **radioiodinated** carbohydrate or a thiolated protein is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method a monoderivatized cyanuric chloride is used to conjugate thiolated protein. **Radioiodinated** residualizing protein conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 14 OF 29 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000007360 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10541347
TITLE: Targeting human cancer xenografts with monoclonal antibodies labeled using **radioiodinated**,

Searcher : Shears 571-272-2528

diethylenetriaminepentaacetic acid-appended peptides.

AUTHOR: Stein R; **Govindan S V**; Mattes M J; Shih L B; **Griffiths G L**; Hansen H J; Goldenberg D M

CORPORATE SOURCE: Garden State Cancer Center, Belleville, New Jersey 07109, USA.

CONTRACT NUMBER: CA39841 (NCI)
CA60039 (NCI)
CA72324 (NCI)

SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10 Suppl) 3079s-3087s.
Journal code: 9502500. ISSN: 1078-0432.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124

AB A new nonmetabolizable peptide approach to the production of residualizing **radioiodine** was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were **radioiodinated** using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, (111)In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per gram of tissue in Calu-3 was 7.9 +/- 4.1% and 18.1 +/- 7.9% ($P < 0.05$) for the conventional 131I- and 125I-IMP-R1-RS7, respectively, and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when 125I-IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing **radioiodine** label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in **radioiodine** incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

L22 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:740238 HCAPLUS

DOCUMENT NUMBER: 132:218942
TITLE: Targeting human cancer xenografts with monoclonal antibodies labeled using **radioiodinated,** diethylenetriaminepentaacetic acid-appended peptides
AUTHOR(S): Stein, Rhona; **Govindan, Serengulam V.**; Jules, Mattes, M.; Shih, Lisa B.; **Griffiths, Gary L.**; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE: Clinical Cancer Research (1999), 5(10, Suppl.), 3079s-3087s
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new nonmetabolizable peptide approach to the production of residualizing **radioiodine** was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were **radioiodinated** using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, 111In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per g of tissue in Calu-3 was 7.9 ± 4.1% and 18.1 ± 7.9% ($P < 0.05$) for the conventional 131I- and 125I-IMP-R1-RS7, resp., and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when 125I-IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing **radioiodine** label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in **radioiodine** incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1999:90010 HCAPLUS
DOCUMENT NUMBER: 130:334689

TITLE: Labeling of Monoclonal Antibodies with Diethylenetriaminepentaacetic Acid-Appended **Radioiodinated** Peptides Containing D-Amino Acids

AUTHOR(S): **Govindan, Serengulam V.**; Mattes, M. Jules; Stein, Rhona; McBride, Bill J.; Karacay, Habibe; Goldenberg, David M.; Hansen, Hans J.; **Griffiths, Gary L.**

CORPORATE SOURCE: Immunomedics Inc., Morris Plains, NJ, 07950, USA

SOURCE: Bioconjugate Chemistry (1999), 10(2), 231-240
CODEN: BCCHES; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The optimal use of **radioiodinated** internalizing monoclonal antibodies (mAbs) for radio-immunotherapy necessitates the development of practical methods for increasing the level of retention of 131I in the tumor. Lysosomally trapped ("residualizing") iodine radiolabels that have been previously designed are based mostly on carbohydrate-tyramine adducts, but these methods have drawbacks of low overall yields and/or high levels of mAb aggregation. We have developed a method using thiol-reactive diethylenetriaminepentaacetic acid (DTPA)-peptide adducts wherein the peptides are assembled with one or more D-amino acids, including D-tyrosine. Two such substrates, R-Gly-D-Tyr-D-Lys[1-(p-thiocarbonylaminobenzyl)DTPA], referred to as IMP-R1, and [R-D-Ala-D-Tyr-D-Tyr-D-Lys]2(CA-DTPA), referred to as IMP-R2, wherein R is 4-(N-maleimidomethyl)cyclohexane-1-carbonyl, were synthesized by preparing functional group-protected peptides on a solid phase, selectively derivatizing the lysine side chain with 1-(p-isothiocyanatobenzyl)DTPA or DTPA dianhydride (CA-DTPA), deprotecting other functional groups, and finally derivatizing the peptide's N-terminus so it contained a maleimide group. **Radioiodinations** of the peptides followed by conjugations to disulfide-reduced mAbs, carried out as a one-vial procedure, resulted in 32-89% overall yields, at specific activities of 1.8-11.1 mCi/mg, with less than 2% aggregation. Two internalizing mAbs, LL2 (anti-CD 22 B-cell lymphoma mAb) and RS7 (an anti-adenocarcinoma mAb which targets EGP-1 antigen), labeled with this procedure exhibited a 2-3-fold better cellular retention in Ramos and Calu-3 tumor cell lines, in vitro, resp., compared to the same mAbs **radioiodinated** with the chloramine-T method. The rationale for the new approach, syntheses, radiochem. and in vitro data are presented.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 1998:163486 HCAPLUS

DOCUMENT NUMBER: 128:215069

TITLE: Stable **radioiodinated** peptide and carbohydrate conjugates with antibodies, and their preparation, for diagnostic and therapeutic use

INVENTOR(S): **Govindan, Serengulam V.**;

Griffiths, Gary L.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; Govindan, Serengulam V.; Griffiths, Gary L.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808548	A2	19980305	WO 1997-US14998	19970827
WO 9808548	A3	19980423		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9743287	A1	19980319	AU 1997-43287	19970827
AU 718859	B2	20000420		
EP 915710	A2	19990519	EP 1997-941363	19970827
EP 915710	B1	20000628		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 194143	E	20000715	AT 1997-941363	19970827
JP 2000517316	T2	20001226	JP 1998-511836	19970827
US 2003220470	A1	20031127	US 2003-359276	20030206

PRIORITY APPLN. INFO.: US 1996-24738P P 19960828
WO 1997-US14998 W 19970827
US 1997-919477 A2 19970828
WO 1997-US23711 A 19971219
US 2000-605873 A2 20000629
US 2000-696740 A2 20001026

APPL.

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable amide bonds are coupled to antibodies. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to antibodies. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to antibodies. In a fourth method, a hydrazide-appended antibody is coupled to a **radioiodinated** carbohydrate, or a thiolated antibody is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method, a monoderivatized cyanuric chloride is used to conjugate thiolated antibody. **Radioiodinated** residualizing antibody conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

L22 ANSWER 18 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:497454 SCISEARCH
THE GENUINE ARTICLE: ZM639
TITLE: Peptide-based residualizing **radioiodine** labels for radioimmunotherapy
AUTHOR: **Govindan S V (Reprint)**; Goldenberg D M; Stein R; Mattes M J; Shih L B; McBride W J; Hansen H J; **Griffiths G L**
CORPORATE SOURCE: IMMUNOMED INC, MORRIS PLAINS, NJ 07950; GARDEN STATE CANC CTR, BELLEVILLE, NJ 07109
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (MAY 1998) Vol. 39, No. 5, Supp. [S], pp. 989-989.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316.
ISSN: 0161-5505.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L22 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:337793 BIOSIS
DOCUMENT NUMBER: PREV199800337793
TITLE: Peptide-based residualizing **radioiodine** labels for radioimmunotherapy.
AUTHOR(S): **Govindan, S. V.** [Reprint author]; Goldenberg, D. M.; Stein, R.; Mattes, M. J.; Shih, L. B.; McBride, W. J.; Hansen, H. J.; **Griffiths, G. L.**
CORPORATE SOURCE: Immunomed. Inc., Morris Plains, NJ 07950, USA
SOURCE: Journal of Nuclear Medicine, (May, 1998) Vol. 39, No. 5 SUPPL., pp. 223P. print.
Meeting Info.: 45th Annual Meeting of the Society of Nuclear Medicine. Toronto, Ontario, Canada. June 7-11, 1998. Society of Nuclear Medicine.
CODEN: JNMEAQ. ISSN: 0161-5505.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L22 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1997:439188 HCAPLUS
DOCUMENT NUMBER: 127:132770
TITLE: Advantage of residualizing radiolabels for an internalizing antibody against the B-cell lymphoma antigen, CD22
AUTHOR(S): Sharkey, Robert M.; Behr, Thomas M.; Mattes, M. Jules; Stein, Rhona; **Griffiths, Gary L.**; Shih, Lisa B.; Hansen, Hans J.; Blumenthal, Rosalyn D.; Dunn, Robert M.; Juweid, Malik E.; Goldenberg, David M.

Searcher : Shears 571-272-2528

CORPORATE SOURCE: The Garden State Cancer Center, Belleville, NJ, 07109, USA
SOURCE: Cancer Immunology Immunotherapy (1997), 44(3), 179-188
CODEN: CIIMDN; ISSN: 0340-7004
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LL2 is an anti-CD22 pan-B-cell monoclonal antibody which, when radiolabeled, has a high sensitivity for detecting B-cell, non-Hodgkin's lymphoma (NHL), as well as an antitumor efficacy in therapeutic applications. The aim of this study was to determine whether intracellularly retained radiolabels have an advantage in the diagnosis and therapy of lymphoma with LL2. In vitro studies showed that iodinated LL2 is intracellularly catabolized, with a rapid release of the **radioiodine** from the cell. In contrast, residualizing radiolabels, such as radioactive metals, are retained intracellularly for substantially longer. In vivo studies were performed using LL2-labeled with **radioiodine** by a non-residualizing (chloramine-T) or a residualizing method (dilactitol-tyramine, DLT), or with a radioactive metal (111In). The biodistribution of a mixture of 125I (non-residualizing chloramine-T compared to residualizing DLT), 111In-labeled LL2 murine IgG2a or its fragments [F(ab')2, Fab'], as well as its humanized, CDR-grafted form, was studied in nude mice bearing the RL human B-cell NHL cell line. Radiation doses were calculated from the biodistribution data according to the Medical International Radiation Dose scheme to assess the potential advantage for therapeutic applications. At all assay times, tumor uptake was higher with the residualizing labels (i.e., 111In and DLT-125I) than with the non-residualizing iodine label. For example, tumor/blood ratios of 111In-labeled IgG were 3.2-, 3.5- and 2.8-fold higher than for non-residualizing iodinated IgG on days 3, 7 and 14, resp. Similar results were obtained for DLT-labeled IgG and fragments with residualized radiolabels. Tumor/organ ratios also were higher with residualizing labels. No significant differences in tumor, blood and organ uptake were observed between murine and humanized LL2. The conventionally iodinated anti-CD20 antibody, 1F5, had tumor uptake values comparable to those of iodinated LL2, the uptake of both antibodies being strongly dependent on tumor size. These data suggest that, with internalizing antibodies such as LL2, labeling with intracellularly retained isotopes has an advantage over released ones, which justifies further clin. trials with residualizing 111In-labeled LL2 for diagnosis, and residualizing 131I and 90Y labels for therapy.

L22 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 1994:503185 HCAPLUS
DOCUMENT NUMBER: 121:103185
TITLE: Technetium-99m, rhenium-186, and rhenium-188 direct-labeled antibodies
AUTHOR(S): **Griffiths, Gary L.**; Goldenberg, David M.; Diril, Habibe; Hansen, Hans J.
CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, 07103, USA
SOURCE: Cancer (New York, NY, United States) (1994),

Not 3 structures

73(3, Suppl.), 761-8
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antibody sulfhydryl groups can act as effective carriers of reduced technetium and rhenium species for radioimmunodetection and radioimmunotherapy. Intact IgG and fragments were labeled with the isotopes and examined in vitro and in vivo. Technetium bound to intact IgG was found to be the most stable species in vitro, but in vivo, clearances of technetium and rhenium bound to intact antibody were similar. Serum clearances were faster than those seen for the corresponding **radioiodinated** antibodies. In vivo clearance rates of the radiolabeled fragments were similar, with kidney uptake and retention seen. Rhenium-labeled antibodies, despite a greater tendency toward in vitro reoxidn. than technetium-labeled antibodies, did not show enhanced kidney clearance in animal models. Rhenium-188 and technetium-99m were obtained from similar generator systems in carrier-free form. Using rhenium-188 spiked with cold rhenium, it was determined that approx. one rhenium atom per mol. of antibody can be conjugated directly. Rhenium-186 also was coupled at almost a 1:1 ratio to antibody. Only radiolysis concerns will limit the amount of rhenium-188 conjugated to antibody. Large doses of antibody will be necessary to deliver rhenium-186 at this isotope's currently available specific activity. Otherwise, higher specific activity rhenium-186, and/or greater loading capacity of rhenium-186 onto antibody, will be needed to generate the type of product that will be usable at a clin. dose of several hundred millicuries.

L22 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 1991:119888 HCAPLUS
DOCUMENT NUMBER: 114:119888

TITLE: Differential endocytosis of CD4 in lymphocytic and nonlymphocytic cells

AUTHOR(S): Pelchen-Matthews, Annegret; Armes, Jane E.; **Griffiths, Gareth**; Marsh, Mark
CORPORATE SOURCE: Chester Beatty Lab., Inst. Cancer Res., London, SW3 6JB, UK

SOURCE: Journal of Experimental Medicine (1991), 173(3), 575-87
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endocytosis of the T cell differentiation antigen CD4 has been investigated in CD4-transfected HeLa cells, the promyelocytic HL-60 cell line, and in a number of leukemia- or lymphoma-derived T cell lines. CD4 internalization was followed using **radioiodinated** antibodies in an acid-elution endocytosis assay, or by covalently modifying cell surface proteins with biotin and analyzing CD4 distributions by immunopptn.; both approaches gave equivalent results. The assays demonstrated that in transfected HeLa cells and in HL-60 cells CD4 was constitutively internalized and recycled in the absence of ligand. Immunogold labeling and electron microscopy demonstrated that CD4 enters cells through coated pin. In contrast to the nonlymphocytic cells, T cell lines showed very little endocytosis of CD4. Measurements of fluid phase endocytosis

and morphometric anal. of the endosome compartment indicated that the endocytic capacities of HeLa and lymphoid cells are equivalent and suggested that the low level of CD4 uptake in lymphocytic cells is due to exclusion of CD4 from coated pits. This conclusion was supported by expts. using truncated CD4 mols., lacking the bulk of the cytoplasmic domain, which were internalized equally efficiently in both transfected lymphocytes and HeLa cells. These results indicate that the cytoplasmic domain of CD4 mediates the different interactions with the endocytic apparatus in lymphoid and nonlymphoid cells. The CD4-associated lymphocyte-specific protein tyrosine kinase p56lck may be involved in preventing CD4 endocytosis in T cells.

L22 ANSWER 23 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:121961 SCISEARCH
THE GENUINE ARTICLE: EZ663
TITLE: DIFFERENTIAL ENDOCYTOSIS OF CD4 IN LYMPHOCYTIC AND NONLYMPHOCYTIC CELLS
AUTHOR: PELCHENMATTHEWS A; ARMES J E; **GRIFFITHS G**; MARSH M (Reprint)
CORPORATE SOURCE: INST CANC RES, CHESTER BEATTY LABS, FULHAM RD, LONDON SW3 6JB, ENGLAND; EUROPEAN MOLEC BIOL LAB, W-6900 HEIDELBERG, GERMANY
COUNTRY OF AUTHOR: ENGLAND; GERMANY
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1991) Vol. 173, No. 3, pp. 575-587.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The endocytosis of the T cell differentiation antigen CD4 has been investigated in CD4-transfected HeLa cells, the promyelocytic HL-60 cell line, and in a number of leukemia- or lymphoma-derived T cells lines. CD4 internalization was followed using **radioiodinated** antibodies in an acid-elution endocytosis assay, or by covalently modifying cell surface proteins with biotin and analyzing CD4 distributions by immunoprecipitation; both approaches gave equivalent results. The assays demonstrated that in transfected HeLa cells and in HL-60 cells CD4 was constitutively internalized and recycled in the absence of ligand. Immunogold labeling and electron microscopy demonstrated that CD4 enters cells through coated pits.

In contrast to the nonlymphocytic cells, T cell lines showed very little endocytosis of CD4. Measurements of fluid phase endocytosis and morphometric analysis of the endosome compartment indicated that the endocytic capacities of HeLa and lymphoid cells are equivalent and suggested that the low level of CD4 uptake in lymphocytic cells is due to exclusion of CD4 from coated pits. This conclusion was supported by experiments using truncated CD4 molecules, lacking the bulk of the cytoplasmic domain, which were internalized equally efficiently in both transfected lymphocytes and HeLa cells. Together, these results indicate that the cytoplasmic domain of CD4 mediates the different interactions with the endocytic apparatus in lymphoid and nonlymphoid cells. We suggest that the CD4-associated lymphocyte-specific protein tyrosine kinase p56lck may be involved in preventing CD4 endocytosis in T cells.

L22 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 1987:28580 HCAPLUS
DOCUMENT NUMBER: 106:28580
TITLE: Identification and quantification of ricin toxin in animal tissues using ELISA
AUTHOR(S): **Griffiths, G. D.**; Newman, Helen; Gee, D. J.
CORPORATE SOURCE: Dep. Forensic Med., St. James Univ. Hosp., Leeds, LS9 7TF, UK
SOURCE: Journal of the Forensic Science Society (1986), 26(5), 349-58
CODEN: FSSJAS; ISSN: 0015-7368
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid, relatively inexpensive, reliable, and straightforward method for the demonstration and quantification of ricin in animal tissues following an injection was developed. The use of **radioiodinated** ricin provided an indication as to where the highest levels of toxin might be found; the highly sensitive and specific use of antibodies in ELISA was employed as an alternative to the more expensive and more tedious procedure of RIA. The injection site, lymphoid tissues, and liver contained detectable amts. of the toxin. In cases where administration of ricin was suspected, confirmation using biopsied tissue samples could enable appropriate remedial measures to be taken. Alternatively, in cases of suspicious deaths, postmortem tissues would be used to identify the presence of toxin in the body and could be of significant value to forensic diagnosis. The advantage of this method over that of immunocytochem. is discussed.

L22 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 1986:455789 HCAPLUS
DOCUMENT NUMBER: 105:55789
TITLE: Immunocytochemical detection of ricin. II. Further studies using the immunoperoxidase method
AUTHOR(S): **Griffiths, G. D.**; Newman, H. V.; Gee, D. J.
CORPORATE SOURCE: Dep. Forensic Med., St. James's Univ., Leeds, LS9 7TF, UK
SOURCE: Histochemical Journal (1986), 18(4), 189-95
CODEN: HISJAE; ISSN: 0018-2214
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Radioiodinated** ricin was injected into rat muscle in vivo to establish the distribution of the toxin at various time intervals after injection. Injection site muscle and paraaortic lymph nodes were selected for localization of ricin by the immunoperoxidase technique. Sections of snap-frozen tissues were fixed using a variety of methods to establish the best protocol for the immunodetection method. This was found to be with an Et2O-EtOH mixture Ricin was detected in tissue at the site of injection taken from rats sacrificed 1, 4, 8, and 24 h after injection and in tissue from animals dying from ricin intoxication after .apprx.30 h. This method, however, failed to demonstrate unequivocally the presence of

ricin in lymphoid tissue which had been indicated by the radiotracer study. The significance of these findings and their relevance to forensic diagnosis are discussed.

L22 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 1979:553228 HCAPLUS
DOCUMENT NUMBER: 91:153228
TITLE: **Radioiodination** of chicken erythrocyte histones H4 and H5 in chromatin
AUTHOR(S): **Griffiths, Garth R.**; Huang, P. C.
CORPORATE SOURCE: Sch. Hyg. Public Health, Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1979), 254(16), 8057-66
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The conformational state of histones in isolated chicken erythrocyte chromatin was studied using procedures developed for probing surface proteins on membranes. Under controlled conditions, only exposed tyrosyl residues react with iodide radicals, generated either by the oxidant, chloramine-T, or the enzyme lactoperoxidase, giving monoiodotyrosine. Using 125I2, the reactive tyrosines in free and bound histones H4 and H5 were compared. The relative extent of iodination of these histones within (H4) and outside (H5) of the nucleosomes was measured after extraction and gel electrophoresis. Each of the histones was further analyzed for the extent of specific tyrosine iodination by separating the tryptic peptides by high voltage electrophoresis. The identity of the labeled peptide was determined by dansylation of the amino acids present in each hydrolyzed peptide. There is a difference in the conformational arrangement of these histones on chromatin and in the free forms, since in chromatin not all tyrosine residues are as accessible for iodination as in the denatured state. Residue 53 of histone H5 for instance is more reactive than residues 28 and 58, indicating that the segments containing the latter residues are involved in either protein-DNA or protein-protein interactions. In histone H4, preferential labeling of 2 of the 4 tyrosines present was also observed

L22 ANSWER 27 OF 29 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 78387472 EMBASE
DOCUMENT NUMBER: 1978387472
TITLE: Confirmation studies of chick erythrocyte chromatin by **radioiodination.**
AUTHOR: **Griffiths G.R.**; Huang P.C.
CORPORATE SOURCE: Dept. Biochem., Johns Hopkins Univ., Baltimore, Md. 21205, United States
SOURCE: Federation Proceedings, (1978) 37/6 (No.2036).
CODEN: FEPRA7
COUNTRY: United States
DOCUMENT TYPE: Journal
LANGUAGE: English

L22 ANSWER 28 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 16

ACCESSION NUMBER: 1978:59884 BIOSIS
DOCUMENT NUMBER: PREV197815003384; BR15:3384
TITLE: CONFORMATION STUDIES OF CHICK ERYTHROCYTE CHROMATIN BY **RADIO IODINATION.**
AUTHOR(S): **GRIFFITHS G R;** HUANG P C
SOURCE: Federation Proceedings, (1978) Vol. 37, No. 6, pp. 1640.
CODEN: FEPRA7. ISSN: 0014-9446.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: Unavailable

L22 ANSWER 29 OF 29 CONFSCI COPYRIGHT 2004 CSA on STN
ACCESSION NUMBER: 78:45316 CONFSCI
DOCUMENT NUMBER: 78087997
TITLE: Conformation studies of chick erythrocyte chromatin by **radioiodination.**
AUTHOR: **Griffiths, G.R.**
CORPORATE SOURCE: Johns Hopkins Univ.
SOURCE: Abstracts (Eng) in Abstracts Volume (Vol. 37, No.6 of "Federation Proceedings," 1 May 78) $12 members or payment of registration fee plus $12 to non-members: Mrs. H. B. Lemp, 9650 Rockville Pike, Bethesda, MD 20014..
Meeting Info.: American Society of Biological Chemists 69th Annual Meeting/American Association of Immunologists 62nd Annual Meeting (782 1085). Atlanta, Georgia. 4-8 Jun 78. American Society of Biological Chemists; American Association of Immunologists.
DOCUMENT TYPE: Conference Article
FILE SEGMENT: DCCP
LANGUAGE: UNAVAILABLE

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